ON THE REACTION OF CELLS AND OF NERVE-ENDINGS TO CERTAIN POISONS, CHIEFLY AS REGARDS THE REACTION OF STRIATED MUSCLE TO NICOTINE AND TO CURARI.

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CONTENTS.

I. INTRODUCTION.

IN a former paper[1] I showed that nicotine stimulates sympathetic nerve cells by a direct action upon them, and I gave reasons for thinking that it does not stimulate pre-ganglionic nerve-endings. I showed also that nicotine can paralyse nerve cells as regards stimulation by nicotine, but I pointed out that the cells might still be excitable by other stimuli and retain some of their functions.

It had been shown in 1889 by Lewandowsky[2] that suprarenal extract had its usual stimulating action upon the iris, eye, and nictitating membrane three weeks after extirpation of the superior cervical ganglion. In consequence, he considered that the extract acted on the muscle and not on the nerve-endings.

This observation was confirmed by myself[3], and to the effects produced

[1] Langley. This *Journal*, XXVII. p. 224. 1901. The possibility that nerve cells may still be capable of stimulation after paralysis by a poison, I had mentioned earlier in discussing the action of nicotine on the sub-maxillary ganglion. (This *Journal*, XI. p. 147. 1890.)

[2] Lewandowsky. *Arch. f.* (*Anat. u.*) *Physiol.* p. 360. 1899.

[3] Langley. This *Journal*, XXVII. p. 237. 1901.

after degeneration of the post-ganglionic fibres were added secretion of saliva, contraction of the blood vessels of the sub-maxillary gland, and erection of hairs. I found that the extract had a specific relation to the sympathetic nerves, inasmuch as its effects were, with one or two doubtful exceptions, such as are produced by stimulating these nerves, and not such as are produced by stimulating cranial or sacral autonomic nerves. This seemed to imply an action on sympathetic nerve-endings, but in view of the production of the above-mentioned effects after degeneration of the nerves, I concluded as in the case of the action of nicotine on nerve cells that the action was direct on the tissues. I pointed out also that adrenalin had a very slight effect on some unstriated muscle innervated by the sympathetic, and that on other unstriated muscle it had no effect at all, so that on the view of its direct action there must be intrinsic differences between different unstriated muscle.

Dixon[1] found that large doses of apocodeine paralysed most post-ganglionic nerve-endings, and abolished the action of adrenalin, although the blood vessels of the intestine still contracted on injection of barium chloride. Similarly Brodie and Dixon[2] found in perfusion experiments on the limbs, kidney, and intestines that a certain amount of apocodeine abolished the vascular constricting action of adrenalin without abolishing the constricting action of barium chloride. They urged therefore that adrenalin must affect the nerve-endings and not the muscle.

These observations—so far as the point at issue is concerned—seem to me of the same nature as that mentioned above on the different effects of adrenalin on different unstriated muscle. Since adrenalin stimulates some unstriated muscle strongly, some little, and some not at all, it follows that adrenalin does not stimulate contractile substance *qud* contractile substance, and it suggests that the action of adrenalin depends upon the presence in the muscle protoplasm of some substance which is not contractile substance.

The observations on the effect of apocodeine do not distinguish between the opposed views of the action of adrenalin, viz., whether it acts directly on muscle or whether it acts on nerve-endings, but they tend to distinguish between two possible forms of the view of direct action. The intrinsic differences in muscle might be referred to differences in the contractile substance, or to differences in accessory protoplasmic substances. On the supposition that barium chloride does

[1] Dixon. This *Journal*, xxx. p. 97. 1904.

[2] Brodie and Dixon. This *Journal*, xxx. p. 476. 1904.

not turn the apocodeine out of its combination, and that it causes contraction in all unstriated muscle in vertebrates, the observations show that the intrinsic differences lie not in contractile substance but in accessory protoplasmic substances.

A second point urged by Brodie and Dixon in favour of the view that adrenalin acts upon nerve-endings is the parallelism in the effects produced by injecting adrenalin and of stimulating the sympathetic nerves. They give further instances of the rule that the effect which adrenalin produces in each tissue is within narrow limits the same as that produced by stimulating the sympathetic, and they showed that in perfusion experiments through the lung, neither stimulation of the sympathetic nerves nor injection of adrenalin causes contraction of the blood vessels. Whilst admitting the weight to be attached to this argument—as I admitted it in my paper in adrenalin—I do not regard it as conclusive. And the view is less simple than at first sight it seems, for adrenalin has very little action in some cases in which the sympathetic nerves have a powerful action. If then adrenalin acts on sympathetic nerve-endings there must be intrinsic differences in the nerve-endings, so that this theory does but transfer the difficulty felt about the existence of intrinsic differences in similar cells in different regions from muscle to nerve-endings[1].

In my opinion the only conclusive evidence is to observe the effect of adrenalin on the unstriated muscle after all the nerve tissue in it has degenerated. As mentioned above Lewandowsky and myself found that the action of adrenalin persisted at a time when (we considered) the nerve-endings had degenerated. In order to account for this fact Brodie and Dixon make two suggestions. First, that the time allowed for degeneration in our experiments was insufficient, and secondly that the nerve-ending is not necessarily a part either of the muscle or the nerve fibre, but a connecting link between them. With regard to the first point, it is unnecessary to give the arguments which lead me to believe that in the cases in question the nerve-endings cease to be irritable in less than seven days, since Elliott[2] has found the reaction of the iris to adrenalin ten months after removal of the superior cervical ganglion, and I have found the usual head effects of adrenalin fourteen and a half months after extirpation of the superior cervical ganglion.

[1] The nature of the action of adrenalin I discuss later, p. 402 and p. 408.

[2] Elliott. This *Journal*, xxxii. p. 401. 1905.

The experiment was as follows:—

In a kitten about 6 weeks old, the left superior cervical ganglion was excised under ether. Fourteen and a half months later (Nov. 1, 1901), the left pupil was still smaller than the right, the difference was marked when the right pupil was large, but slight only when it was small; the left nictitating membrane and eyelids showed slight signs of paralysis. The left ear vessels were moderately contracted, they did not dilate, as did those of the right ear, when the animal ran about. The colour of the nose and lips was the same as the two sides.

The actual production of anæsthesia by chloroform did not cause reversal in the size of the pupils; the pupils dilated at first and then became moderately contracted; but a short time after complete anæsthesia the left pupil became larger than the right, and for the most part remained so, sometimes it was very much larger, sometimes only slightly or not perceptibly. Similar reversal occurred in the nictitating membrane and eyelids.

Some connective tissue occupied the place of the left superior cervical ganglion; stimulation of the cervical sympathetic had no effect, the post-ganglionic strands of the ganglion were isolated and stimulated, these also had no trace of effect on the pupil, nictitating membrane, eyelids, vessels of ear, and hairs of face area.

The sclerotic of the left eye was exposed and stimulated,—there was marked local contraction of the sphincter but no trace of dilatation. Stimulation of the sclerotic of the right eye at once caused marked local dilatation, as well as contraction.

3 c.c. of the suprarenal extract, T. 1 in 6, described in my Paper on "Adrenalin," were injected. The effects were:

Great dilation of left pupil, followed by moderate dilation of right.
Left eyelids wide open, and nict. memb. retracted; similar but less effect on the right.
Ears became pale, the relative effect was not observed.
Two drops of saliva from the submaxillary gland.

Three minutes after the injection, the left pupil began to decrease, the right was already small. There was still some secretion from the submaxillary gland.

Stimulation of the submaxillary gland artery had no effect, the chorda tympani at once caused secretion.

The left tympanic bulla was broken through and strong currents applied to the region overlying the anterior post-ganglionic sympathetic fibres—no sympathetic effect was obtained.

A similar result as regards the iris, I obtained in another experiment in which the superior cervical ganglion had been removed for 6½ months.

The first suggestion then can, I think, be definitely put on one side. And if the action of adrenalin is not on nerve-endings in the case of the tissues innervated by the superior cervical ganglion, it is, I think, practically certain that its action is not on nerve-endings in the case of other tissues innervated by sympathetic ganglia. There is in fact more or less decisive evidence in other cases. Thus Brodie and Dixon (*op. cit.*) found that three months after section of the great majority of the vaso-motor nerves to the hind limb (section of the crural and sciatic nerves) adrenalin caused contraction of the vessels in the perfused limb. And Elliott (*op. cit.*) has obtained adrenalin action on the blood vessels

of the intestine, on the bladder, and on the retractor penis after degenerative section of the sympathetic nerves supplying them. Lastly Magnus and myself[1] found that adrenalin and other substances had their usual effect on the small intestine after nearly complete (in the ileum probably complete) degenerative section of the intestinal nerves.

The second suggestion of Brodie and Dixon is somewhat vague since it is not clear what is meant by saying that the connecting link is not necessarily a part of either nerve or unstriated muscle. The phrase seems to imply a structure which has a vitality independent of both. Histologically no such structure exists. On the other hand the phrase may mean that the connecting link is part both of muscle and nerve and can be kept alive by either. This view assumes continuity between nerve and muscle. So far as I know there is no evidence that in cells which certainly unite, any substance exists which is special to the point of union and can be kept alive by either cell. Such a view should, I think, be taken only as a last resort. In the case of nerve and unstriated muscle, we are not driven to this, for since the connecting link does not degenerate on nerve section, the obvious conclusion is that it is part of the unstriated muscle.

It must however be noticed that a connecting link of a different kind from that contemplated by Brodie and Dixon may be present in the 'terminal network' described by Bethe[2] and others. Bethe considers that the small cells on this network are nerve cells, and that the network has a vitality independent of the nerve fibres running to it. On this view the nerve-endings in the unstriated muscle would not degenerate on extirpation of the sympathetic ganglia. For my part I take the cells to be connective tissue cells and believe that the nervous portion of the network (or plexus) degenerates on section of the fibres running to it. At present however there is not conclusive proof of this degeneration, though some evidence has been given by Fletcher[3].

Elliott brings forward further and most striking evidence that adrenalin stimulates tissues which are stimulated by sympathetic nerves and these only. This leads him to look on adrenalin as acting on some substance common to sympathetic nerves. He finds, however, that degeneration of the nerves does not diminish the action of adrenalin, and as he considers that the axon endings degenerate, the substance affected by adrenalin must be in trophic connection with the muscle.

[1] Langley and Magnus. This *Journal*, xxxiii. p. 47. 1905.

[2] Bethe. *Allg. Anat. u. Physiol. d. Nervensystems*, (Leipzig) p. 78. 1903.

[3] Fletcher. *Proc. Physiol. Soc.* xxxvii. 1898. (This *Journal*, xxii.)

This as I have pointed out above is, I think, the same as saying that it is part of the muscle. But in view of the close relation of adrenalin to sympathetic nerves, and because he considers it improbable that the varying action of adrenalin can be due to intrinsic differences in the muscle, he concludes that when sympathetic nerves unite with unstriated muscle they cause the formation in it of a new substance, the myo-neural junction, and it is this which is acted upon by adrenalin.

Now supposing that nervous connection does cause in the muscle the formation of a new substance, this does not make the new substance any the less part of the muscle. The fundamental fact of Elliott's view is then, I think, the same as mine, viz. that adrenalin acts directly on muscle. It goes a step farther in localising the muscle substance acted on to the immediate neighbourhood of the nerve ending. And it differs from my view in considering that the muscle substance acted on is not an intrinsic part of the muscle cell but a part developed in it in consequence of nerve union. These questions I shall consider later. For the present I am only concerned with the evidence that various substances act directly on peripheral cells, and not on the nerve fibres ending in them.

It was noted by Anderson and myself[1] incidentally to other work, that pilocarpine caused secretion in the pads of the cat's feet six weeks after removal of a portion of the sciatic nerve and when regeneration of the nerve had not taken place.

Lastly it has been shown by Anderson[2] that after removal of the ciliary ganglion pilocarpine still causes contraction of the pupil and that this constriction is prevented by atropine. After atropine, the sphincter of the iris is still capable of contraction; consequently he concludes that both atropine and pilocarpine act on some substance of the unstriated muscle and not on the axon-endings, nor on the contractile substance.

From the above account it is clear that there is good evidence that certain poisons produce their normal effects on nerve cells, on unstriated muscle, and on glands after degeneration of the nerve fibres which run to them. In the case of the nerve cells there is no question of any cellular element intervening between the nerve fibres and the nerve cells. In the case of unstriated muscle and glands such cells are, it is true, said to exist, but the evidence for their existence is not generally accepted.

There is then more or less satisfactory evidence that the substance

[1] Langley and Anderson. This *Journal*, xxxi. p. 423. 1904.

[2] Anderson. *Proc. Physiol. Soc.* p. xlix. 1905. (This *Journal*, xxxii.)

on which a number of poisons act is part of the peripheral cells. It seemed to me eminently desirable to test this question on some other tissue. This I have done on striated muscle.

II. THE ACTION OF NICOTINE AND CURARI UPON SOMATIC NERVE-ENDINGS AND UPON SKELETAL MUSCLE.

The stimulating action of nicotine on certain muscles of the fowl.

In a former paper[1] I stated that the muscular contraction known to be produced in the fowl by nicotine appeared to me to be chiefly due to a stimulation of the nerve-endings. This observation I have followed up since it suggested a further means of investigating the nature of nerve-endings.

If a small dose of nicotine as 0·5 to 1 mgrm. is injected into the jugular vein of an anæsthetized fowl, lying on its back and unfastened, the legs are slowly and gradually extended and pass into a state of more or less marked tonic rigidity. They remain extended without support for a varying time—usually 8 to 12 minutes,—when they slowly relax and sink. The neck and head are drawn towards the thorax; but I have not noticed any marked rigidity of the neck. The wings are slightly, but only slightly, drawn towards the thorax, they do not become rigid, and can throughout be easily moved passively in any direction. The respiration ceases for a time, possibly in consequence of rigidity of some of the respiratory muscles. In consequence of this, dyspnœa occurs, if artificial respiration is not kept up, and may cause movements, especially of the wings. Usually after a short pause there are respirations which gradually resume the normal rhythm. But the respiration may be insufficient in the early stages and lead to death. The dose will also cause opening of the eye and movement of the feathers.

The minimal dose required to produce an appreciable effect was usually in my experiments about 0·2 mgrm. But the minimal effective dose, and the dose required to produce marked rigidity in the legs, vary in different cases, and apparently vary with the species. In one or two instances the muscular effect produced by 1 mg. of nicotine was only slight.

With larger doses I have always started artificial respiration before the injection. The effect up to 50 mgrm. of nicotine is to make the

[1] Langley. This *Journal*, xxx. p. 239. 1903.

contraction more rapid (though the rate of contraction is always very slow compared with that caused by electrical stimulation), and to prolong somewhat the duration, so that 20 minutes may elapse before the extended legs begin to fall. But the increase in duration is not directly proportional to the increase in the amount of nicotine given.

Section of the sciatic and of the crural nerves on one side makes no essential difference in the changes occurring in the legs. Some differences in time of onset and duration occur, but these are only such as might be caused by the severance of muscles necessary in cutting the nerves, by alterations in blood supply, and by difference in the muscles on the two sides. No doubt in the absence of anæsthetics, nicotine stimulates the central nervous system as it does to a greater or less extent in other vertebrates, but the effect described here is not of central but of peripheral origin.

Since in the fowl most of the muscles of the leg are red, and those of the wing are white, the difference in the action of nicotine upon the leg and on the wing naturally suggests that the poison causes tonic contraction in red muscles but not in white.

As a rule this is certainly the case. On exposing the muscles and injecting intravenously a dose of nicotine (as 5 to 10 mgrms.) large enough to ensure a fairly rapid contraction, the red muscles of the leg can be seen to shorten, whilst no movement is perceptible in the white muscles of the wing. I have taken also a graphic tracing of one of the white muscles of the wing; the injection of nicotine caused no trace of movement of the lever. But I have not investigated this question systematically. In one experiment on the rabbit, nicotine had no stimulating effect on the red muscles.

In order to analyse the phenomenon further I have made observations by the graphic method, using the gastrocnemius muscle. This muscle served my purposes, but for certain points of investigation it is not satisfactory. The upper end contains a considerable admixture of white muscle, and although this part of the muscle contracts with nicotine, it is not certain that the white fibres do. Moreover, owing to the short course taken by many of the fibres, and their complicated arrangement, local contractions, especially of the upper part, may occur, which are obvious to the eye, but which exert so little pull on the tendon Achilles as to barely move the lever attached to it.

Method. The fowls were first given chloroform, and during the rest of the experiment A.C.E. mixture by a tracheal tube. A warm water

bag was used to keep up the temperature. Injections were made into the jugular vein. When the contraction of the gastrocnemius of one side only was to be observed, the fowl was placed on its side. The sciatic nerve (and sometimes also the crural) was cut high in the thigh. The internal peroneal nerve was tied and cut in the lower part of the thigh. The muscles were cleared from the upper part of the femur, and the thigh bone clamped. The tendon of the gastrocnemius was tied, the skin over the muscle cut, and the lower $\frac{2}{3}$rds of the muscle freed from its attachments. The leg was then extended, the clamp on the femur fixed to a stand, and the leg also clamped above and below the ankle. The stands holding the leg clamps were clamped to the table. The thread attached to the tendon of the gastrocnemius was tied to a thread passing over a wheel and fastened to a lever writing on kymograph paper, so that a contraction of the muscle caused a rise of the point of this lever. A warm flannel was usually hung over the muscle a little above it. At the beginning of an experiment the sciatic was stimulated in order to see whether the contraction of the muscles supplied by it caused any movement of the lever; usually there was a slight movement of 2 to 3 mm. (a rise or fall according to other conditions of the experiment), due to the muscles of the thigh or the lower leg pulling on the upper part of the gastrocnemius. It seemed to me better to retain this small source of error in the form of the gastrocnemius curve than to run the risk of interfering with the circulation by severing the lateral attachments of the muscle throughout.

When the contractions of both gastrocnemii were recorded, two methods were tried after the necessary dissection. (*a*) The fowl was placed on its back, and the legs clamped, inclined upward, or (*b*) it was placed ventral surface downwards, the sternum resting in a wedge-shaped trough. By this method the legs were usually not sufficiently far from the body to prevent a trifling movement of the gastrocnemius with each respiration (cp. Fig. 3); but the muscle is less exposed than by the former method. This position was adopted when the blood-pressure in the femoral artery was taken on one side and the gastrocnemius contraction on the other. In all the tracings the lever multiplied the contraction 4 times, the weight employed was usually 10 grams.; the extent of reduction of the tracings is given in the description of the figures.

The nicotine contraction of the gastrocnemius, as shown in the tracing, has the general features mentioned above as seen in the muscles of the leg generally, namely, slow shortening and prolonged duration.

The form of the curve, however, varies considerably and I have not definitely settled to what the differences are due.

The usual type of curve is that given in Fig. 1—which shows also the effects of single induction shocks. The greater part in the rise in the curve occurs in about 30 secs., there is then a slow further rise lasting two or more minutes, this is maintained for a minute or two and passes into a relaxation, which is slow throughout, especially at the beginning and at the end.

Sometimes the slow rise after the primary one is much abbreviated, *i.e.* the maximum height is more quickly attained.

Not infrequently the very slow rise gives way to a fall as soon as it has reached its maximum, so that the summit of the curve though very flat topped is not a straight line.

A second type of curve is that in which the maximum height of the curve—attained in 20 to 30 secs.—gives way almost at once to a partial fall lasting about 20 secs.; this is succeeded either by the usual slow fall, or by a straight line and then a slow fall. Fig. 6*b* shows a curve of this type, though not in a very developed form. This type is more common when nicotine is given in large doses and on repeated injection. When the leg is adequately fixed, I attribute this type of curve to a late contraction of other muscles of the leg pulling down the upper part of the gastrocnemius, but it may be due to partial relaxation of some of the fibres of the muscle itself. If the leg is not clamped below the ankle this type of curve is commonly obtained in a marked form. If the leg is not fixed at all, or only fixed below the ankle, the curve commonly has two apices, showing that the different muscles attain their maxima at different times.

The first dose of nicotine in my experiments always led to some contraction remainder (cf. Fig. 1); the return to the original length was not attained in an hour, the longest time I have waited for it, but it must be noted that the weight applied was a light one. When the obvious descent of the lever has ceased, a second small dose of nicotine will again cause contraction, the contraction being of rather less height and duration, and the injection can be repeated many times with progressive decrease in effect. When a small dose of nicotine has no or only a slight effect, a considerable one can still be obtained by injecting a large dose, as 20 mgs., and when this becomes ineffective, a still larger amount, as 50 mgs., will cause more or less contraction. When a given dose ceases to produce an effect, it will usually produce one if an interval of about half-an-hour to an hour is allowed before

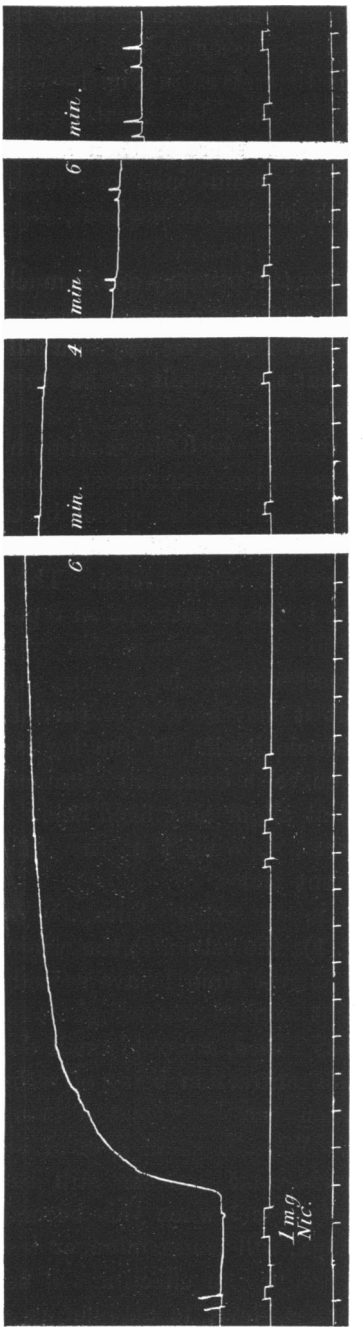

Fig. 1. Usual form of curve of gastrocnemius contraction caused by injecting nicotine, and effect of induction shocks. 1 mg. nicotine injected into the jugular vein. The signal (not set accurately under the gastrocnemius lever) marks the passage of induction shocks into the muscle (secondary coil at 1·5 cm.), first the make, then after 3 or 4 secs. the break shock. Time markings show 10 second intervals. Reduced by about ⅓rd.

repeating the injection. In fact as regards repeated doses, nicotine stimulates the striated muscle much as it stimulates nerve cells; and much as adrenalin stimulates certain unstriated muscle cells. The chief characteristic of the stimulative action of nicotine on striated muscle is its long duration. Now, as is known, nicotine paralyses somatic motor nerves. After about 10 mgs. of nicotine have been given, faradic stimulation of the internal peroneal nerve causes very little contraction of the gastrocnemius, and on repetition, this is, as a rule, only a twitch at the beginning of the stimulation. Sometimes the contraction is only a feeble flicker in the upper part of the muscle[1] which has no effect in the tracing. After about 15 mgs. of nicotine have been given, the internal peroneal nerve is completely paralysed.

The different muscles of the limb, however, require somewhat different amounts of nicotine to produce complete paralysis of the nerves.

I have already said that a large dose of nicotine will cause contraction after much more than 15 mgs. have been given. It follows then that injection of nicotine, after the internal peroneal nerve has been paralysed, still causes contraction. Indeed if small successive amounts of nicotine are given, there is nothing in the curves to indicate the point where paralysis occurs.

Direct stimulation after nicotine. Inhibition by the galvanic current.

After nicotine has paralysed the internal peroneal nerve, direct stimulation of the muscle with the interrupted current, using the ordinary electrodes, has naturally only a local effect and the movement of the lever is comparatively slight. Owing to the anatomical arrangement of the muscle fibres, stimulation on the inner surface near the lower end gives a greater effect on the lever than stimulation elsewhere. The effect is not, so far as I have seen, appreciably further decreased by any dose of nicotine (200 mgrs.), provided the circulation remains good; but I have not made exact experiments on the point. It is certain, however, that nicotine in large doses does not paralyse the muscle for direct tetanic stimulation.

For experiments upon the comparative effect of stimulation before, during, and after the nicotine contraction, I pierced the muscle with

[1] In one case a series of tiny waves of contraction coursed down a strip of the upper part of the muscle.

platinum electrodes (swinging easily in their connected wires), one about the middle of the muscle, the other about a centimetre from the lower tendon.

Strong induction shocks (1 Dan. cell, du Bois machine, sec. coil at 0) give but slight effects on the tracing. In Fig. 1 an example is given of the effect obtained. At the height of the nicotine contraction the induction shocks give no effect on the tracing, though a local twitch of the muscle may be distinct to the eye. As the muscle relaxes—if a small dose of nicotine only has been given—the induction shocks have again an effect and naturally the break before the make shock, until the normal rise is approximately obtained, and this occurs whilst the muscle is still in a state of slight contraction (cp. Fig. 1). When the internal peroneal nerve is paralysed by nicotine or by curari the effect of single induction shocks is very slight. The interrupted current causes contraction at every stage of the nicotine curve.

The make and the break of a galvanic current (4 Daniell cells in series) gives moderate contractions (Fig. 2 *a*, *b*). During the greater part of the prolonged contraction produced by nicotine, the make of the current causes partial relaxation which lasts until

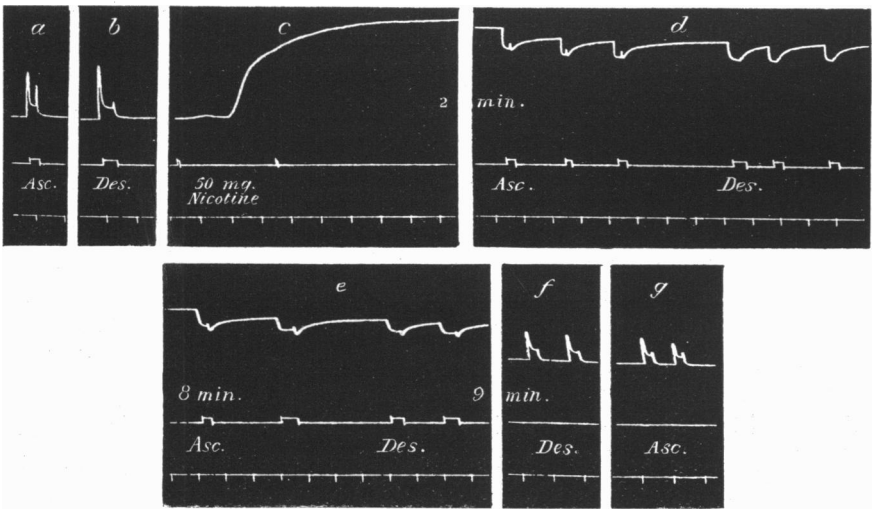

Fig. 2. Inhibition of contraction by the constant current. Nerves paralysed by 15 mgs. curari. Make and break stimulation with 4 Daniell's cells. (*a*) Ascending. (*b*) Descending. (*c*) Injection of 50 mgs. nicotine. Interval of 2 mins. (*d*) Ascending current three times, and descending current three times. Interval of 8 mins. (*e*) Ascending twice, descending twice. Interval of 9 mins. (*f*) Descending twice. (*g*) Ascending twice. Reduced ½.

the break of the current, *i.e.* it causes partial inhibition (Fig. 2 *d*). The inhibition is marked both with the ascending current (positive pole near tendon) and with the descending current (negative pole near tendon). A slight twitch is produced at the break of the current, this is more marked when the current is ascending than when it is descending (Fig. 2 *d*). As the muscle relaxes, the break twitch of the descending current increases (Fig. 2 *e*), then a make twitch begins, though there is still some inhibition during the passage of the current; the make and break contractions increase and the inhibition decreases until the normal response is obtained (Fig. 2 *f*, *g*). On injecting nicotine anew, inhibition can again be obtained.

It will be remembered that Biedermann clamping in the middle a veratrinised frog's sartorius in a double myograph, obtained make anodic inhibition in one half, and make kathodic contraction in the other. In the fowl's muscle the state is no doubt essentially the same, but the inhibition predominates so much over the contraction, that the muscle as a whole elongates considerably.

The mutual effects of nicotine and curari on muscle.

Since curari prevents nerve stimulation from having an effect, but does not itself cause muscular contraction, and nicotine, although also preventing nerve stimulation from having an effect, does cause muscular contraction, it seemed possible that the latter might act on some substance or structure placed more peripherally than that on which the former acts.

I have made experiments in three ways:—

a. Curari is given after the administration of anæsthetics at the beginning of an experiment; a small dose of nicotine is then given and the effect compared with that produced by the same dose in other experiments in which curari is not given.

b. Nicotine is given, then curari, and then again nicotine; the relative effects of the two doses of nicotine is compared with their relative effects in other experiments in which curari is not given.

c. Curari is given during a contraction brought about by nicotine, and the effect on the contraction noted.

In the fowl, the somatic nerves are paralysed by about 15 mgs. of curari. In two experiments by method (*a*) 10 mgs. of curari were given and then 1 mg. of nicotine. In one case the nicotine had no

effect on the gastrocnemius tracing, and in the other it caused a very slight rise only. As I have said above, 1 mg. of nicotine, in all the cases in which curari is not given, induces contraction, and in nearly all cases considerable contraction of the gastrocnemius (cf. Fig. 1). Hence the slight contraction produced in these two experiments indicates that curari in a dose insufficient to paralyse completely the somatic nerves reduces nearly to zero the stimulating effect of a small dose of nicotine.

Since, however, the extent of contraction produced by a small amount of nicotine varies in different fowls, I took for comparative observations two young cockerels of the same species and brood, almost indistinguishable from one another. In these the stimulating action of nicotine was much less than usual, and the antagonistic effect of curari on the nicotine contraction was greater than usual. As they illustrate also the results obtained by methods (*b*) and (*c*), and the effect of large doses, I give some details of them.

The contraction produced by 1 mg. of nicotine was a very slow gradual contraction (Fig. 3 A); whilst the curve was still rising 10 mg. of curari was injected and this caused in about 15 secs. a fall in the curve (cf. Fig. 3 A). In the 2nd experiment 10 mgs. of curari were first given, and then 1 mg. of nicotine; this caused only a trace of contraction (Fig. 3 B).

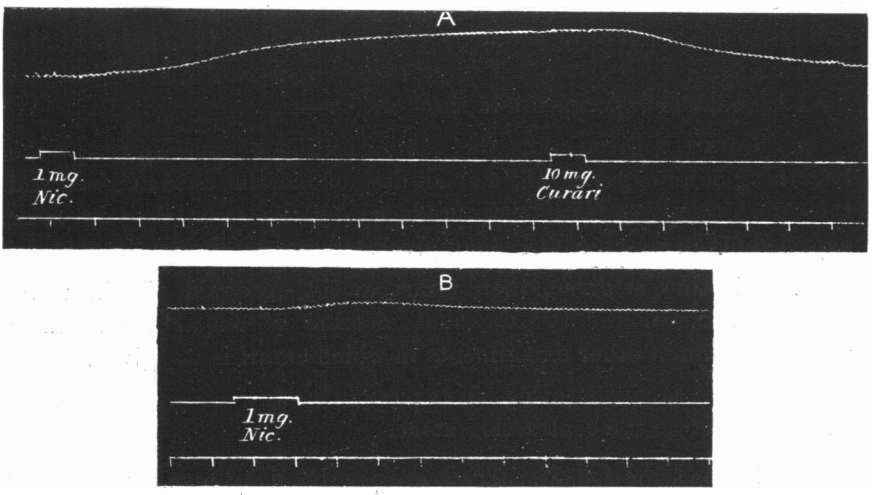

Fig. 3. Mutual effect of curari and nicotine. A. Exp. 1. Curari given after nicotine. B. Exp. 2. Nicotine given after curari. Reduced $\frac{1}{3}$ nearly.

Later, larger injections of nicotine had in both experiments but a slight effect (cf. protocols following), but with a sufficient dose a strong contraction was produced in both cases. In one experiment the contraction was allowed to take its course and it lasted many minutes: the first part of the curve is given in Fig. 4. In the other experiment curari was injected, and it caused gradual relaxation, as shown in Fig. 5.

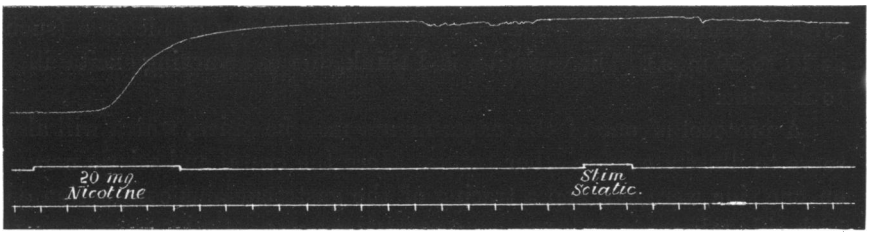

Fig. 4.

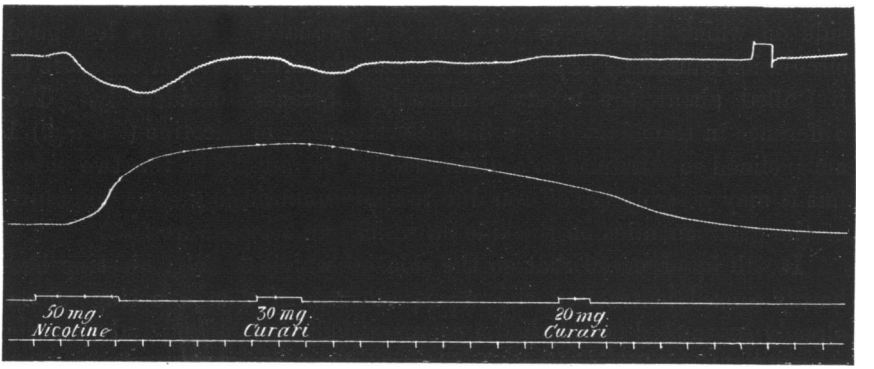

Fig. 5.

Figs. 4 and 5. Reduced ½. Mutual effect of curari and nicotine. Fig. 4 (Exp. 2). Contraction produced by a large dose of nicotine. Fig. 5 (Exp. 1). A similar contraction annulled by curari. The upper curve gives the blood-pressure.

Exp. 1.		Contraction of gastrocnemius
	1 mg. nicotine	—gradual, slight (Fig. 3 A)
	10 mgs. curari	—decrease (Fig. 3 A)
12 mins.	10 mgs. nicotine	—trace
20 ,,	25 mgs. nicotine	—slight, prolonged
37 ,,	50 mgs. nicotine	—good (Fig. 5)
	30 mgs. curari	—slow, decrease
	20 mgs. curari	—quicker decrease
90 ,,	50 mgs. nicotine	—slight, slow

Exp. 2.		Contraction of gastrocnemius
	10 mgs. curari stimulate sciatic	—small
9 mins.	1 mg. nicotine	—very slight (Fig. 3 B)
38 ,,	3 mg. nicotine	—very slight
39 ,,	20 mgs. nicotine	—very slight
60 ,,	20 mgs. nicotine	—good (Fig. 4)
	stimulate sciatic	—no effect
80 ,,	10 mgs. nicotine	—slight, slow

The blood-pressure was taken in both experiments, it remained high throughout.

From these experiments it is, I think, clear that curari and nicotine are antagonistic in large as well as in small amounts, and that the extent of contraction is proportional to the relative amounts of the two poisons. I have made a considerable number of experiments by methods (*b*) and (*c*) and always with the same general result, but I have found wide variations in the degree of antagonistic action of curari on the nicotine contraction. And in no other instance have I found curari to have so great a counter-action on comparatively large doses of nicotine (such as 10 to 20 mgs.). The variation is, I think, due to a varying excitability to nicotine.

A protocol of one of the experiments may be given, which will also serve to illustrate some other points. Here the crural and sciatic nerves on one side were cut, and a tracing of the gastrocnemius contraction on each side taken.

It will be seen (Fig. 6) that the contractions on the two sides differed in minor points; the slower beginning of the effect of injection on the side on which the nerves were cut was probably due to a less good circulation caused by exposure of the femoral artery, for on exposure or if pulled about the artery commonly contracts considerably. The difference in the effect of the first effective dose of nicotine (0·5 mg.) I am inclined to attribute to a difference in the muscle on the two sides, but it may possibly have been due to some unnoticed greater exposure of the gastrocnemius on the side on which the nerves were cut.

It will be observed that on the side on which 0·5 mg. nicotine had hardly caused contraction, the subsequent dose of 2 mgs. acting on an already contracted muscle had a comparatively little effect, and that the curve is of the 2nd type mentioned above (p. 383).

In mammals curari beyond a certain amount causes a great fall of blood-pressure, and it seemed possible that the relaxation of the nicotine contraction caused by curari might be due to a diminution in the blood supply to the muscle. But this is not the case. For when the femoral artery is clamped during a nicotine contraction the contraction continues undiminished for a considerable time, and the relaxation when it occurs is much less and is more gradual than that produced by curari. Moreover in the experiments in which I have taken the blood-pressure, very little or no fall of blood-pressure has been produced by curari; an instance is given in Fig. 5.

It may be noted in passing that nicotine when first injected causes a rise of blood-pressure, as in the mammal, but the rise is less steep and in general not so great as in the mammal. After a certain amount has

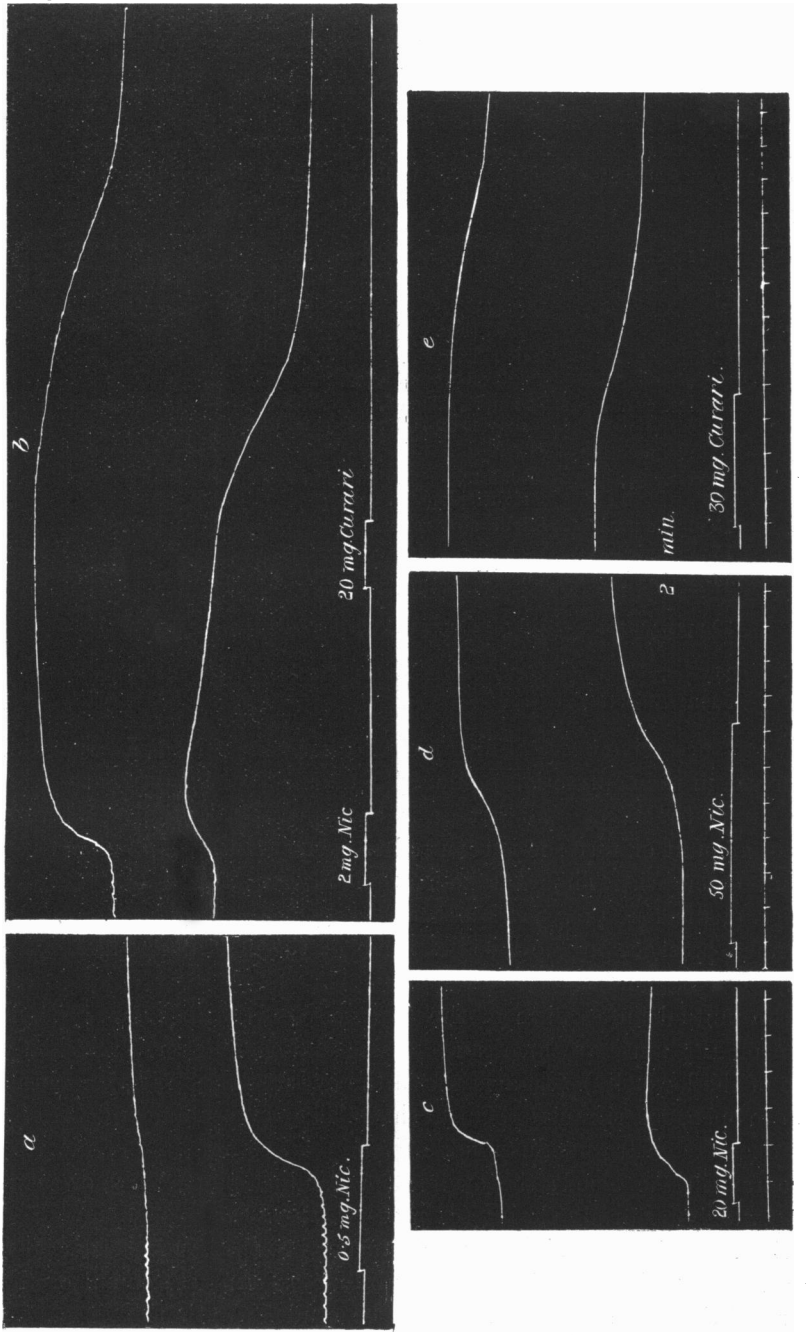

Fig. 6. Reduced + $\frac{1}{3}$. Time in 10 secs.

been given, it causes a temporary fall of blood-pressure (cf. Fig. 5); accompanying this there may be a slowing of the heart-beat.

Exp. 3. The general arrangements were as given above under 'Methods.' On the left side, the crural and sciatic nerves were cut in the upper part of the thigh, the muscles being freely severed to expose the nerves. On the right side, the nerves were uncut. In Fig. 6, the upper tracing is that of the left, and the lower that of the right gastrocnemius.

Time after beginning of preceding injection	Injection	Contraction as shown on tracing	Eye
	$\frac{1}{10}$ mg. nicotine	0	Remains closed
2 mins.	$\frac{1}{2}$,,	Left side, slow, slight. Right side, good (Fig. 6 *a*)	Opens
6 ,,	2 mgs. ,,	Left side, good. Right side, moderate; curve of type 2 (Fig. 6 *b*)	Opens a little wider
$1\frac{1}{3}$,,	20 mgs. curari	Gradual relaxation, quicker and greater on right side (Fig. 6 *b*)	Slowly closes
$6\frac{2}{3}$,,	2 mgs. nicotine	0	0
5 ,,	20 mgs. ,,	Moderate, begins rather sooner on right side (Fig. 6 *c*).	Slowly opens
$3\frac{1}{2}$,,	15 mgs. curari	Slight, slow relaxation.	Slowly shuts
$6\frac{1}{2}$,,	15 mgs. nicotine	Very slight, slow contraction	Very slowly opens $\frac{1}{2}$
2 ,,	50 ,,	Moderate to good, a little quicker on right side (Fig. 6 *d*)	Opens widely
4 ,,	30 mgs. curari	Slow relaxation, quicker on right side (Fig. 6 *e*)	Slowly closes $\frac{1}{3}$
8 ,,	25 ,,	Slight relaxation on right side	Slowly closes $\frac{2}{3}$
15 ,,	50 mgs. nicotine	0	Opens widely

When successive doses of nicotine are given, there is, as I have said, a decrease in the contraction produced. When successive doses are given after curari, the effect is additive, a fact which supports the view that a certain amount of nicotine is required to overcome the effect of a given amount of curari. Thus I take it that in Exp. 2 the 2nd dose of 20 mgs. of nicotine produced a strong contraction, partly because of the continued presence in the blood of some of the first almost ineffective dose.

The mutual antagonism of the two poisons is readily seen in their action on the muscles which cause closing and opening the eye (chiefly those of the lower lid). In anæsthesia the eyes are shut, nicotine causes them to open, curari causes them to shut. They respond more delicately than does the gastrocnemius muscle to the relative amounts of nicotine and curari in the blood; the eyelids moving just perceptibly, or separating widely, or firmly closing (cf. protocol, Exp. 3).

The mutual antagonism can only mean that the two poisons act on the same protoplasmic substance or substances. Any statement of the nature of this action must at present be crude. With this proviso, I

take it that the action consists in a combination of the alkaloid with the protoplasm. Curari in combining leads to diminished excitability and does not stimulate; nicotine in combining also leads to diminished excitability, but it stimulates in combining. Which combination is formed depends upon the relative amounts of the two poisons.

In order to explain the fact that nicotine prevents stimulation of the nerves from causing contraction, but will itself cause contraction on a further dose, we might suppose,

(*a*) that nicotine combines with several substances, and that it has different affinities for these substances. This view implies that the substances of less affinity for nicotine are not stimulated by nervous impulses;

or (*b*) that nicotine combines with one substance, but with different degrees of completeness according to the amount of nicotine present. With incomplete combination the excitability is diminished sufficiently to prevent the nerve impulse from having any effect, but as further combination can take place, nicotine can still stimulate. When combination is complete a further large dose of nicotine cannot stimulate, and in fact does not cause contraction.

I am inclined to adopt the latter supposition.

The general relation of nicotine and curari to muscle is the same as that I pointed out some years ago for the relation of atropine and pilocarpine to the salivary glands[1]. Physiologically the difference between the action of the two pairs of alkaloids is, that in the case of the salivary glands, the affinity of the stimulating agent (pilocarpine) is less than that of the simply paralysing agent (atropine); whilst in the case of the fowl's muscle, the affinity of the stimulating agent (nicotine) is greater than that of the simply paralysing agent (curari).

THE EFFECT OF DEGENERATIVE SECTION OF THE SCIATIC NERVE.

On this point I have made five experiments, cutting the peroneal nerves (in Exp. 4 the internal peroneal nerve only) and removing 1 to 3 centimetres, the length of the piece varying roughly with the time allowed for the degeneration of the nerve. This time was in Exp. 1, 6 days; Exp. 2, 8 days; Exp. 3, 27 days; Exp. 4, 38 days; Exp. 5, 40 days.

[1] This *Journal*, I. p. 367. 1878. See also Marshall. This *Journal*, XXXI. p. 120. 1904.

In three other fowls the nerves were cut; one (Exp. 6, 25 days) was killed by a ferre which escaped from its cage; another (Exp. 7, 58 days) died of tubercular lung disease; the third (Exp. 8, 72 days) died of tubercular liver disease. Ether was used as an anæsthetic, the tendon of the ilio-fibularis muscle was cut through at its lower, and for a short distance along its posterior, edge and reflected. The muscles were pulled apart, and the sciatic nerve (consisting of the external and internal peroneal nerves joined together) was exposed. The sciatic was cut, the peripheral end pulled up, and the external and internal peroneal nerves isolated as far as the knee-joint and there cut; the intermediate piece of nerve was removed. Aseptic methods were used, and the wounds healed readily.

The section of the peroneal nerves affected the power of movement to very different extents in the several experiments. In all the experiments except 6 and 7 the fowls soon learnt to balance on the sound leg, and to move about without much difficulty; on the operated side the whole of the foot from the ankle downwards was placed on the ground in hopping or walking, but in experiments 1 and 3, the leg was first flexed and kicked out behind once or twice before being placed on the ground. In Exp. 6 the fowl which was large, was unable to balance, and fell forward in trying to walk. In Exp. 7 the balancing and power of walking was very imperfect. Section of the internal peroneal nerve alone, though modifying the movements, improved little, if at all, the power of progression.

The final observation was conducted in the manner already described. The sciatic was in all cases cut about two centimetres centrally of the neurome, and the peripheral end stimulated, the gastrocnemius being exposed and observed. In no case did the sciatic cause any trace of contraction in the muscle, so that functional regeneration had not taken place. Nor did the stimulation cause contraction in the other muscles of the lower leg in the four cases in which the external as well as the internal peroneal nerve was cut. In Exp. 5 the sciatic caused slight contraction in the lower part of the thigh near the neurome, indicating some outspread of fibres from the neurome into the immediately adjoining muscle.

The gastrocnemius of each side was weighed except in Exp. 2. The weights in grams are given in the following Table. The numbers are probably slightly inaccurate, since no special care was taken to cut out exactly corresponding parts of the tendons.

	Time allowed for degeneration	Sound side	Side with nerves cut	Percentage loss in weight
Exp. 1.	6 days	10·0	9·7	3·0
Exp. 3.	27 „	6·0	3·1	48·3
Exp. 4.	38 „	10·4	4·9	52·9
Exp. 5.	40 „	7·8	3·1	60·3
Exp. 6.	25 days	4·3	3·4	21·0
Exp. 7.	58 „	3·3	1·8	45·5
Exp. 8.	72 „	2·3	1·1	56·6

It will be seen that, as was to be expected, section of the nerves

caused atrophy of the gastrocnemius, roughly proportional to the duration of the paralysis. The less percentage decrease in Exps. 6, 7 and 8 is probably due to some atrophy of the gastrocnemius on the sound side; for in Exp. 6 the sound leg was used very little, and in Exp. 7 much less than in the other fowls; in Exp. 7 there was some wasting of all the muscles, and this was very great in Exp. 8.

In all five experiments, injection of nicotine caused contraction of the gastrocnemius in the normal manner, and repeated contractions were obtained by repeated injections. I have already said that the responsiveness of the gastrocnemius to nicotine varies in different fowls. Consequently considerable caution must be exercised in comparing the response of the denervated muscle with that of the normal muscle. But the results of the experiments tend to show that the responsiveness to nicotine is increased by denervation. Thus in Exp. 1, $\frac{1}{10}$ mg. of nicotine caused a good contraction[1], and in Exp. 5, 1 mg. of nicotine (cp. Fig. 7) caused a more rapid contraction than I have seen with that dose in any normal muscle.

It will be remembered that increased excitability to certain stimuli after section of peripheral nerves has been shown in several tissues. Thus the super-normal dilation of the pupil described by Budge and Langendorf, as occurring in certain conditions after removal of the superior cervical ganglion, is due according to Lewandowsky and Anderson[2] to increased excitability of the dilatator pupillæ. Elliott has shown[3] that the dilatator pupillæ, the blood vessels of the ear, and of the intestines, the heart, the retractor penis, the arrectores pilorum all contract better with small doses of adrenalin after degenerative section of their nerves (sometimes of the pre-ganglionic nerves). Further, it has been found by Anderson[4] that dyspnœa and some alkaloids cause greater contraction of the sphincter of the pupil on the side in which the ciliary ganglion has been removed for some days or weeks than on the normal side. Indications of some increase of inhibitory response in the intestine after section of the mesenteric nerves were obtained by Magnus and myself[5].

In the denervated muscle, curari still exercised an antagonistic effect

[1] No contraction was obtained with $\frac{1}{10}$ mg. nicotine at the beginning of Exp. 5.

[2] Anderson. This *Journal*, xxx. p. 290, 1903, where other references are given.

[3] Elliott. This *Journal*, xxxii. p. 438. 1905.

[4] Anderson. *Proc. Physiol. Soc.* p. xlix. 1905 (This *Journal*, xxxii.); This *Journal*, xxxiii. p. 156. 1905.

[5] Langley and Magnus. This *Journal*, xxxiii. p. 34. 1905.

on the nicotine contraction, but the antagonism was distinctly less than normal. The effect is shown in the protocols of Exps. 1 and 3 given below.

As we have seen, contraction of the normal gastrocnemius can be repeatedly obtained by repeated injections of nicotine. The denervated muscle behaves in the same way. In Exp. 2 five successive injections of 2 mgs. of nicotine were made at intervals of 10 to 15 minutes, and each caused moderately strong contractions.

Exp. 1.

Time after previous injection	Injection	Contraction
	0·1 mg. nicotine	Slight to moderate
7 mins.	0·5 ,,	Good
5 ,,	15 mgs. curari	Slight increase in rate of relaxation
5 ,,	1 mg. nicotine	Moderate
15 ,,	15 mgs. curari	
5 ,,	1 mg. nicotine	Trace only
7 ,,	5 mgs. ,,	Slight to moderate
12 ,,	20 mgs. ,,	Good and fairly rapid
10 ,,	50 mgs. curari	
7 ,,	20 mgs. nicotine	Slight to moderate

After the first injection of curari the eye remained closed throughout.

Exp. 3.

Time after previous injection	Injection	Contraction	Eye
	1 mg. nicotine	Good	Opens
15 mins.	1 ,,	Good, less than before	Opens widely
7 ,,	10 mgs. curari		Closes
6 ,,	2 mgs. nicotine	Moderate	Remains closed
6 ,,	10 mgs. curari		
4 ,,	2 mgs. nicotine	Trace	Remains closed
10 ,,	5 ,,	Slight	,, ,,
45 ,,	2 ,,	Trace	,, ,,
2 ,,	20 ,,	Good, quick rise	Opens slightly
15 ,,	20 mg. curari		Closes
5 ,,	50 mg. nicotine	Moderate	Remains closed

In Exp. 5, in which the nerves had been cut for 40 days, curari was injected during the nicotine contraction. The slight effect is shown in Fig. 7. The first injection of curari (10 mgs.) produced no obvious effect; the second injection (20 mgs.) quickened somewhat the relaxation.

The effect of the constant current (6 Daniell cells in series) was then tried; the make, both of the ascending and of the descending current,

caused strong quick contraction (Fig. 8). Five mgs. of nicotine were injected, twenty-five minutes after the injection of 1 mg. just mentioned, this caused a quick, strong contraction of the gastrocnemius without obvious contraction of the opposite leg or opening of the eye. During the continuance of the contraction the muscle was stimulated several times with the ascending and descending constant current. At first, there were make and break twitches, and during the passage of the current considerable inhibition with the descending current, slight with

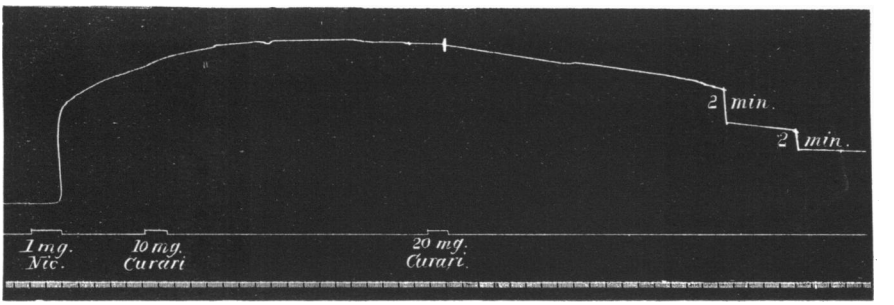

Fig. 7. Reduced $+\frac{1}{2}$. Denervated muscle. Effect of nicotine and of curari after nicotine. Time in secs. omitting every tenth.

the ascending. Later, the current being sent through the muscle for a longer period, the break twitch of the descending current disappeared, the inhibition produced by the ascending current was minimal, but there was a slight inhibition on breaking the current (cp. Fig. 8). After this the muscle barely reacted to strong single induction shocks, and with strong tetanising currents gave but a rise of 1 cm. on the tracing. This and the slight effect obtained with single and repeated induction shocks in other experiments after several injections of nicotine indicates that the denervated muscle is much more easily fatigued than normal.

Discussion of results.

The experiments given in the foregoing section show that in certain muscles of the fowl the degeneration of the nerves supplying the muscles does not essentially alter the contraction caused by nicotine. Sokolow[1] has shown that the axon-endings of the striated muscles of the frog degenerate after section of the nerves. In Exp. 2 (8 days after section

[1] Sokolow. *Arch. de Physiol.* p. 308. 1874.

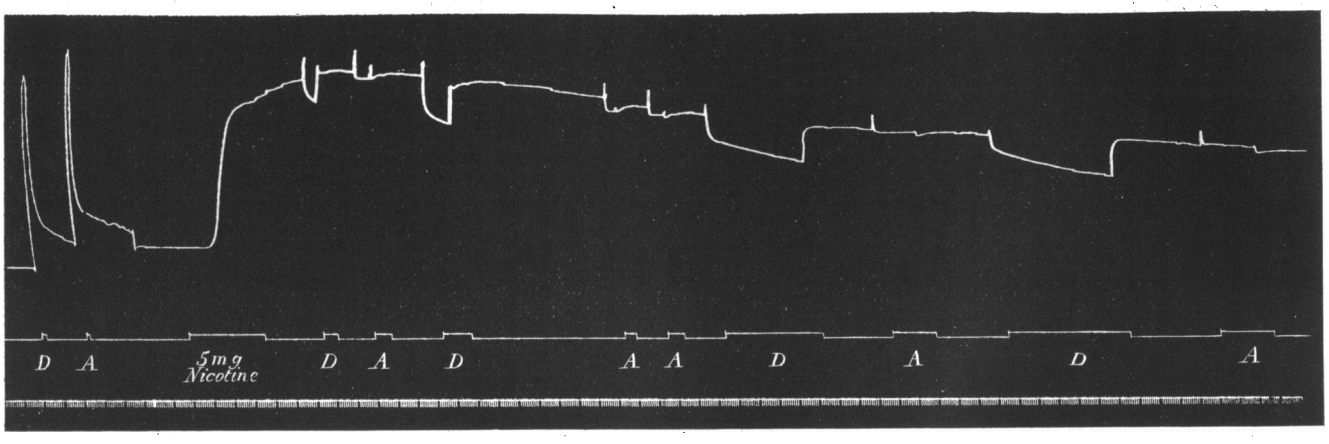

Fig. 8. Reduced $+\frac{1}{3}$. Denervated muscle. Effect of constant current during the nicotine contraction. *A*—Ascending current, *D*—Descending current.

of the nerves), and in Exp. 3 (27 days after section of the nerves), corresponding portions of several of the muscles on the two sides were treated with gold chloride and formic acid. Axon-endings were found on the sound side, but none on the side with degenerated nerves, although here and there degenerated nerve fibres could be traced up to the muscle fibres. It would certainly be more satisfactory if the progressive changes in the nerve-endings of birds and mammals after section of the nerves were known, but I do not think there can be any doubt that the axon-endings do degenerate.

I conclude then that nicotine acts upon the muscle substance, and not upon the axon-endings.

Ruffini and Apathy have described 'ultra-terminal' nerve fibrils proceeding from the obvious axon-endings in muscles in man. It might be supposed that these, if they exist, can be kept alive by the muscle, but, as I have said above, it seems to me simpler to regard all that is kept alive by the muscle in the muscle itself as part of the muscle.

It has been shown above that curari acts upon the same substance as nicotine. It follows then that curari acts upon the muscle substance and not upon the axon-endings.

Since, in the normal state, both nicotine and curari abolish the effect of nerve stimulation, but do not prevent contraction from being obtained by direct stimulation of the muscle or by a further adequate injection of nicotine, it may be inferred that neither the poisons nor the nervous impulse act directly on the contractile substance of the muscle but on some accessory substance.

Since this accessory substance is the recipient of stimuli which it transfers to the contractile material, we may speak of it as the *receptive substance* of the muscle.

Now nicotine does not stimulate all the muscles of the bird, and it does not, so far as we know, stimulate any in the mammal. Moreover, whilst curari "paralyses" the motor nerves in mammals, it does not paralyse them in the crayfish. It follows then that there are considerable differences in the receptive substance in different muscles. And it seems to me probable that we must regard the embryonic muscle protoplasm as forming several receptive substances responsive to different chemical stimuli.

The relation between the receptive and the contractile substance is clearly very close, and, on the general lines of Ehrlich's immunity theory, it might be supposed that a receptive substance is a side chain molecule of the molecule of contractile substance, but at present there

does not seem to me to be any advantage in attempting to refer the phenomena to molecular arrangement.

III. Remarks on the receptive substance of cells, and its connection with nerve-endings.

If the view given in the preceding section is true in the particular case of striated muscle, it gives a firm basis for making deductions with regard to the mode of action of nervous and chemical stimuli in other tissues. I will first give the deductions which seem to me to follow logically, and then consider the conclusions arrived at by Elliott in his able paper already referred to in the Introduction.

1. Starting then from the view that in striated muscle the action of nicotine is on certain receptive substances in the muscle, the facts given in the Introduction as to the action of nicotine on nerve cells, of adrenalin, atropine, and pilocarpine on certain unstriated muscle and glands, after nerve degeneration, give good ground for believing that in these cases also the poisons act on the receptive substances of the cells.

The gap in the evidence in the case of nerve cells is the inadequacy of the evidence that the nerve cells retain any function after paralysis by nicotine or other chemical body. The gap in the evidence in the case of unstriated muscle and glands is that satisfactory evidence of degeneration of the axon-endings after nerve section is lacking.

Further, the action of secretin on the pancreas[1] obviously suggests a direct action on receptive substances in the cell. And if adrenalin and secretin act in this way, it may fairly be inferred that the other internal secretion substances, as thyroidin and the various stimulating chemical bodies formed by the generative organs, act in the same manner.

I conclude then that in all cells two constituents at least must be distinguished, (1) substance concerned with carrying out the chief functions of the cells, such as contraction, secretion, the formation of special metabolic products, and (2) receptive substances especially liable to change and capable of setting the chief substance in action. Further, that nicotine, curari, atropine, pilocarpine[2], strychnine, and most other alkaloids, as well as the effective material of internal secretions produce their effects by combining with the receptive substance, and not

[1] Bayliss and Starling, This *Journal*, xxviii. p. 325. 1905.

[2] Previous to the experiments on degeneration of nerves mentioned in the Introduction I advocated the view that atropine and pilocarpine act on nerve-endings.

by an action on axon-endings if these are present, nor by a direct action on the chief substance.

2. It is well known that in the body some unstriated muscle is strongly influenced by sympathetic nerves, some slightly, and some not at all. The differences in innervation are more or less clearly advantageous; and we may infer that the present condition has been reached by a slow process of natural selection. No doubt a considerable factor in bringing natural selection into play has been the varying use of the several nervous connections.

The varying use might be caused by a variation in the conditions external to the tissues actually concerned. But it is difficult to see what external conditions could lead to disuse or slight use in particular cases, as in the arteries of the bladder of most mammals, and in different portions of the gastric arteries of the rabbit. Some other factor seems to me to be required.

This factor, I take it, is probably the inherent tendency to chemical variation in the cell protoplasm, so that different receptive substances are formed, the responsiveness of which to nervous stimuli varies. Thus I think it probable that with equal nervous connection, one unstriated muscle might be strongly influenced, and another very slightly, and another not at all.

Some light may be thrown on this question by a comparison of the degree of action of nerves on unstriated muscle and the amount of nerve supply. From preliminary observations I have made, it appears to me that there is no constant relation between the two, and that unstriated muscle which is not appreciably affected by nerve stimulation may have an appreciable nerve supply.

Now this factor, if it exists in the case of the connection of nerve fibres to unstriated muscle, must exist—though its value will vary—in all cases of the connection of nerve-endings with cells, including those of the nervous system. And thus it might account for the effect of nerves on certain pigment cells of amphibia which is absent in the case of other connective tissue cells.

The argument given above holds, I think, whether the nerve-endings are in continuity or only in contiguity with the cell, though in the former case some further problems arise, as whether the linking substance of nerve and cell is the substance which is stimulated by nerve impulses or independent of it. But I am inclined to believe that actual union does not occur. The embryological evidence of union seems to me quite

inconclusive as regards the condition in the adult, for it is readily conceivable that chemical differentiation should lead to a separation of units which are at first only potential. In the adult the histological evidence seems to me strongly against continuity. And experiment gives one fact against it, viz. that nicotine applied to a sympathetic ganglion does not cause an axon reflex. Since nicotine stimulates the sympathetic cell, the impulse would, I think, travel back to the axon if the two were continuous.

3. Different peripheral tissues vary in the continuousness of the functional state. In the case of those which are connected with nerve fibres, some are in a constant state of slight activity, brought about by nervous stimuli; it is a familiar fact that this causes the tone of striated and of certain unstriated muscle. In experiments made some years ago[1] on the union of the central end of the vagus with the peripheral end of the cervical sympathetic nerve, I found that after functional union had occurred, the vagus exerted a tonic action on those structures on which the cervical sympathetic normally exerts a tonic action. The result indicated that the normal tone is partly dependent on the condition either of the superior cervical ganglion or of the peripheral structures. And the results given in this paper render it probable that this condition is the degree of responsiveness of the receptive substance of the peripheral structures. Thus there would be two factors in producing tone, viz. the intensity of the nervous stimuli, and the responsiveness of the receptive substance; and stimuli incapable of producing tone in one tissue might be capable of producing it in another.

4. The varied effects produced by poisons show that the receptive substance varies in different cells (cp. p. 408). But the effects show also that the receptive substance connected with the cells of any one class have frequently some common characters, and that they differ more or less from the receptive substances connected with the nerve fibres of any other class. The preferential action is very marked in the case of adrenalin.

The similarity in the receptive substance connected with any one class of nerve fibres, and the dissimilarity in that connected with different classes is, I consider, due to the nerve fibres of any one class becoming connected with cells at approximately the same period in their phylogeny when the conditions are approximately the same, and

[1] This *Journal*, XXIII. p. 255. 1898.

the chemical characters of the cells are the same within comparatively narrow limits. The connection once made will tend by use to fix the characters of the receptive substance.

The case in which nerve fibres from two systems form nerve-endings in one tissue presents no difficulty if the nerve fibres end in adjoining cells. If they end in the same cells, the matter is less simple, but I should suppose that the first nerve connection tends to fix the characters of the receptive substance most in the immediate neighbourhood of the ending, and that chemical variation still occurs elsewhere in the cells so that when another system of nerves forms nerve-endings it meets with a different receptive substance.

5. When a nerve is in functional connection with a cell the receptive substance it affects will, as I have just said, tend to become fixed, and in such cases there will probably also be a tendency for the receptive substance to be localized in the neighbourhood of the axon-ending.

In the cases in which a tissue has a nerve supply both from the sympathetic and the para-sympathetic system[1] there is evidence of considerable, if not exclusive, localisation on the assumptions that efferent impulses are of the same character and that the two sets of nerve fibres end in the same and not in adjoining cells. For stimulation of the two sets of nerves produces different effects either in kind or degree. Evidence still stronger is afforded by the discovery made by Dale[2], and confirmed by Elliott[3], that chrosotoxin can paralyse the motor sympathetic fibres running to a tissue, without paralysing the motor para-sympathetic fibres running to it.

It is possible that the same holds for all other nerve-endings, but it does not necessarily follow that this is so. In the case of striated muscle I hope to settle the question by observing under the microscope the behaviour of the teased-out muscle fibres when irrigated with nicotine.

In the cases in which there is localisation, the receptive substance may conveniently be called the *synaptic substance*, since it can be applied to all forms of cells.

6. I have formerly adduced evidence[4] (as have others) that in-

[1] I use the word para-sympathetic for the cranial and sacral autonomic systems.

[2] Dale. *Proc. Physiol. Soc.* p. lviii. 1905. (This *Journal*, xxxii.)

[3] Elliott. This *Journal*, xxxii. p. 401. 1905.

[4] Langley. *Text-book of Physiology*. Edited by Schäfer, ii. p. 672. 1900. For the evidence as regards the inhibitory fibres of the heart cp. Gaskell. *Ibid.* ii. p. 203.

hibitor, as motor, nerves produce their effect by a direct action on the tissue in which they end. Elliott (*op. cit.* p. 436), starting from the view that nervous impulses primarily affect the myo-neural junction, has pointed out that if the nervous impulses in inhibitory and motor nerves are the same, it would be the function of the myo-neural junction to determine whether the effect of a nervous impulse is inhibitory or not, and that both inhibitory and motor substance might be present in one myo-neural junction. Granting the assumption, the conclusion seems to be inevitable, and I take it that in general an increase or decrease of function in a cell brought about by chemical or nerve stimulation depends upon the presence in the cell of different receptive bodies.

The assumption is justified in so far as it seems unlikely that a difference in wave-length or frequency of the nervous impulse can cause the difference between increase and decrease of function.

If, however, the axon of a motor nerve were the negative pole of its cell, and the axon of an inhibitory nerve were the positive pole of its cell, one might expect, on the analogy of the effect of the galvanic current, that the nervous impulse passing down the former would cause contraction, and that the nervous impulse passing down the latter would cause inhibition. But even then it would be difficult to explain inhibition on stimulating a nerve cut off from its cell.

Some light may be thrown on the question by cross union of post-ganglionic nerves belonging to the same system and to a different system. The investigation unfortunately presents considerable difficulties.

7. The results given above suggest that the axon-endings are the same as any other part of the axon (differing from the rest of the cell), and that a chemical substance will only affect the axon-endings if they affect the axon itself. But the observations of Anderson on the relation of the ciliary nerves to the sphincter of the iris raise a doubt on this point. Anderson[1] finds that eserine has no stimulating effect on the ciliary ganglion or the short ciliary nerves, but that its constricting action on the pupil disappears two days after section of the nerves. After a time, eserine again causes constriction, and this is again abolished by section of the nerves. In this case then it appears clear either that eserine stimulates axon-endings, in which case they must differ from the pre-terminal axons, or that the mere connection of axon-endings with the sphincter muscle causes in the muscle the formation of a special receptive substance. It is to be noted that both pilocarpine and

[1] Anderson. *Proc. Physiol. Soc.* p. xlix. 1905. (This *Journal*, xxxii.) and Paper about to be published in this *Journal*.

atropine act on the sphincter after degeneration of the ciliary nerves, so that the receptive substance as a whole does not disappear.

We may now pass to a consideration of the view given by Elliott as to the mode of action of adrenalin on unstriated muscle, a view which is applicable to all cases of nerve-endings.

Elliott considers that the substance which is stimulated by adrenalin is not an intrinsic part of the muscle, but is developed from the muscle in consequence of its union with a sympathetic fibre. This substance is formed at the junction of the nerve and muscle, and establishes continuity between them, hence he calls it after Brodie and Dixon the myo-neural junction[1].

This view is based on the parallelism which exists between the action of adrenalin and the effect of stimulating the sympathetic nerves. The tissues acted on by adrenalin are varied, and *primâ facie* the only common point is their innervation by a particular kind of nerve fibre. The natural deduction is that the feature which is common, or nearly common, to them, viz., that of reacting to adrenalin is due not to the tissues themselves but to their connection with sympathetic nerves.

It is also in favour of this view that adrenalin is found in cells which in development are intimately connected with the sympathetic system. Further, the limitation in the action of some other poisons to certain systems of nerves is *primâ facie* strongly in favour of Elliott's contention. Thus nicotine acts on pre-ganglionic and on somatic nerve connections. Since the nerves of both systems arise from the spinal cord, and have, as shown by Anderson and myself, some power of cross union, it is easier to believe that the common characters which allow the nicotine action, reside in the nerve fibres, than in the very different tissues in which they end.

Nevertheless as the facts stand at present I do not feel able to adopt it. My chief reason is that section of the sympathetic nerves does not cause any atrophy of the substance acted on by adrenalin. If this substance were produced in consequence of the union of the nerve with the unstriated muscle, it would, I think, certainly diminish and probably rapidly disappear when the union ceased. Neither in nerve cells, nor unstriated muscle, nor striated muscle is there any evidence that nerve degeneration causes more atrophy of the receptive than it does of the chief substance; there is indeed some reason for believing that

[1] The term is used by Brodie and Dixon in a vaguer sense, see Introduction.

in striated muscle the reverse is the case. Moreover the result is the same whether the nerves are cut in young animals (cf. Exp. given on p. 377) or in the adult.

As it seemed possible that observations on the time at which poisons begin to take effect on the embryo might throw some light on the question, I tried the effect of adrenalin, nicotine, and strychnine on the chick, in various stages of development.

It is to be noticed on the one hand that the differentiation of the cell substance, for example in a muscle cell, certainly takes time, and it is conceivable that it would not be completed before the nerves become functional; and on the other hand, that the nerve fibres might exert a chemical action on the cell before they transmit nervous impulses.

The action of muscarine and atropine on the embryonic heart has been described in some detail by Pickering. He found that in the mammal[1] muscarine caused slowing, and atropine removed the slowing in the earliest stages, a fact which is decidedly against the view that the substance acted on is formed by nervous impulses, and, though less decidedly, against the view that it is formed by any kind of nerve action. He did not however obtain the same result in the chick[2]; in this case muscarine did not slow the heart till about the 8th day.

The most striking result of my own observations was the cessation of the contraction of the amnion on adding adrenalin. The contractions of the amnion are caused by a thin layer of unstriated muscle; so far as I know no nerves have been found in it, but it is possible that it has not been adequately investigated. Nicotine increased the rhythmic contractions of the amnion or set them going if the amnion was quiescent, and it seemed clear that this action occurred locally on local application. In the adult, nicotine does not affect unstriated muscle. Strychnine had no effect on the amnion up to the 12th day, after this date the amnion was not noticed.

Nicotine on and after the 13th day caused repeated twitching of the limbs, and at times local twitches in the various muscles, also opening of the eye, and movement of the jaw. Its paralysing action was not great, but it increased towards the end of the incubation period. All of these effects may have been due to an action on the central nervous system, for according to Preyer[3] twitching of the limbs can be obtained on the

[1] Pickering. This *Journal*, xx. p. 183. 1896.

[2] Pickering. This *Journal*, xviii. p. 488. 1895. (Some earlier references are given in this paper.)

[3] Preyer. *Specielle Physiologie des Embryo*. Leipzig. 1885.

12th day by stimulating the spinal cord. On the 21st day (one exp. only) after destruction of the lumbar cord, application of nicotine was followed by tonic extension of the hind limbs. The action of the alkaloid in the earlier stages (6th to 12th day) varied. Twitchings of the limbs were obtained in nearly all cases by applying 1 p.c. nicotine, but not up to the 9th day by applying 0·1 p.c. Sometimes a slow tonic contraction of the body or of the hind limbs was obtained, but this did not occur with sufficient constancy to allow any definite conclusion as to its cause. On the whole I conclude that the characteristic action of nicotine in the leg muscles of the adult is a late development, and that nicotine is an earlier excitant of the muscle than nerve stimulation. According to Preyer (*op. cit. supra*) direct faradic stimulation causes a very weak contraction on the 7th day, a weak reflex may perhaps be present on the 11th day, stimulation of the spinal cord gives twitching of the limbs on the 12th day and tetanus on the 15th.

Strychnine had no effect up to the 10th day, on the 14th it caused repeated twitching. (No observations on the effect of strychnine were made on the intervening days.)

The eggs after exposing the embryo were usually placed in a dish of hemp-seed and kept at 38° C. in a warm chamber.

Two or three small drops of the solution were allowed to run either on the allantois or on the amnion. The solutions used were adrenalin $\frac{1}{2000}$ to $\frac{1}{1000}$ (hemisine of Burroughs and Wellcome, once adrenalin of Parke, Davis & Co.), nicotine 0·1 to 1 per cent., strychnine hydrochlorate 1 to 2 per cent. The solutions were kept at 38° C.

Adrenalin usually stopped the movements of the embryo as well as of the amnion. That adrenalin stops the amnion movements is perhaps best shown by observing the egg by transmitted electric light, and injecting the adrenalin through a small hole in the shell and shell membrane. The inhibition is apparently accompanied by loss of tone, for the embryo sometimes sinks.

Preyer did not observe twitches of the limbs till the 7th day. I have seen active twitches (after adding nicotine) in an embryo of 5 days 18 hours.

On the 18th day (after nicotine), there was rhythmic erection and depression of the feathers of the head and neck; the rhythm being often different in adjoining feathers.

Electrical stimulation (faradic and galvanic current) I usually tried after having added nicotine; up to the 14th day I did not obtain any certain effect, except on the amnion. On the 21st day, an hour after the beginning of the experiment and after nicotine, stimulation of the sciatic had no effect, but contraction of the muscles and movement of the feathers were readily obtained by direct stimulation for another hour. In this and other late embryos ether was given on opening the shell.

The argument from the action of poisons on which Elliott's view is based is, as I have said, *primâ facie* very strong. But a closer examination shows, I think, that the argument is inconclusive even when the action of adrenalin alone is considered, and involves great difficulties when the actions of several poisons are compared.

I will take first the action of adrenalin. The argument depends upon the parallelism between the action of adrenalin and the action of sympathetic nerves. It is clear that the argument becomes inconclusive in proportion as the parallelism is incomplete. Thus if adrenalin only produced the same effect as the sympathetic in a single case, no stress could be laid upon it. Now the parallelism though considerable is incomplete[1]. Elliott suggests for these exceptions that the response to adrenalin depends on the number of nervous stimuli[2]. This however seems to me essentially to alter the argument. The fundamental fact in this case is that a substance capable of reacting to adrenalin is formed in the myo-neural junction as the result of nervous stimulation; and it is inferred from this that the rest of the myo-neural junction which is readily responsive to nerve stimulation but not readily responsive to adrenalin is formed in some way by the union of the nerve with the muscle. Supposing the fact to be established, the inference is clearly not a necessary consequence.

It is certain from the action of adrenalin that all the myo-neural junctions of the sympathetic nerves have not the same chemical characters. Further, sympathetic nerves produce motor and inhibitory effects in very varying degree in different tissues, so that on the view that inhibition and contraction depend on the presence of different substances in the myo-neural junctions, hardly any two myo-neural junctions can have the same chemical nature.

Other differences in the synaptic substance connected with any one system of nerves are shown by other poisons. Thus according to Dale[3] chrysotoxin paralyses most post-ganglionic sympathetic motor fibres, but has very little effect on the fibres of this system running to the heart and to the dilator of the pupil, and no appreciable effect on the similar pilo-motor fibres. Nicotine in the fowl stimulates the synaptic substance of some somatic nerves but not that of others. Nicotine in vertebrates generally, stimulates nearly all sympathetic nerve cells, but it has no appreciable stimulating action on the superior cervical ganglion in the rabbit, nor on the ciliary ganglion in the cat. Atropine readily paralyses the post-ganglionic cranial secretory fibres, but has very little effect on the similar vaso-dilator fibres.

[1] The facts I have mentioned earlier (This *Journal*, xxvii. p. 254–5. 1901), and they are dealt with more fully by Elliott (*op. cit.*).

[2] If this were so, one would expect the responsiveness to adrenalin to increase on nerve stimulation. I have only made one experiment on the point, but I did not find any such increase.

[3] Dale. *Proc. Physiol. Soc.* p. lviii. 1895. (This *Journal*, xxxii.)

Both stimulation and paralysis imply a combination of the poison with some substance, so that an action of whatever nature implies some similarity in the substance acted on. The different physiological effects produced by the combination may be regarded as due to minor differences, such as the presence of different radicles in (or the existence of different molecular associations of) the substances primarily affected. Thus a broad chemical similarity may exist in the connections of different nerve systems, though physiologically their behaviour is different. And it is, I think, conceivable that combinations should be formed by poisons which have no effect observable by our present methods; and in that case there may be still wider similarities between the connections of different systems of nerves.

When we compare the action of different poisons on different systems of nerves we have evidence not only of differences in the synaptic substance of any one system of nerves, but of resemblances between the synaptic substance of different systems.

Thus in the cat nicotine paralyses somatic nerve fibres more readily than it paralyses some pre-ganglionic fibres, but less readily than it paralyses others, so that in this respect some pre-ganglionic synaptic substance more nearly resembles the synaptic substance of somatic nerves than it does the synaptic substance of other pre-ganglionic fibres.

Apocodeine according to Dixon first paralyses pre-ganglionic fibres, then it paralyses somatic nerve fibres and post-ganglionic vagus fibres in the heart, lastly it paralyses certain but not all post-ganglionic sympathetic fibres. Here then certain cranial autonomic synaptic substance and certain sympathetic synaptic substance are more alike than either is to the synaptic substance of its own system of nerves.

Atropine readily paralyses most post-ganglionic cranial autonomic fibres, but it has a comparatively slight effect on the cranial viscero-motor fibres, and little if any on the cranial vaso-dilator fibres. On the other hand it readily paralyses the sympathetic sudoriferous fibres, and in rather larger amount (in the cat) the sympathetic salivary fibres. Then it passes (in the rabbit at any rate) to the sacral autonomic fibres which cause drawing down of the rectum. Thus atropine shows greater resemblances in the synaptic substances of some of the nerves of three classes than obtains between the synaptic substance of any one class.

These and similar instances in the action of other poisons show, I think, that the characters of the synaptic substance as a whole do not depend upon the system of nerves with which it is connected.

Hence the simple view, which is at first sight suggested by the preferential action of poisons, that a nerve fibre of a given system on union with a cell gives rise in it to a definite substance, is untenable.

This however does not necessarily exclude the central point of Elliott's theory, viz. that the myo-neural junction is formed as a conse-

quence of union of nerve and muscle, but it seems to me to necessitate a modification in the statement of it. We must suppose, either that in each class of nerves there are a number of varieties, and that each variety gives rise to its own kind of synaptic substance, or that the nerve fibres in each class are the same, but give rise to different synaptic substances because the cells in which the nerve fibres end are different. The former hypothesis shifts the differences from cell to nerve fibre[1]; the latter allows intrinsic differences in the cell, but considers that these have no functional value unless nerve union occurs. Both have the stumbling-block in their way, that the synaptic substance does not degenerate on degeneration of the nerve fibres.

Lastly we might suppose that the synaptic substance is partly formed independently by the cell, and partly formed in it by a chemical action of the nerve fibre. *A priori* much might be said for this view. But the only instance in the action of the poisons mentioned above which tends to show that a nerve fibre can give rise to a special substance in a cell is, I think, the action of eserine described by Anderson (cf. p. 404). This substance degenerates on degeneration of its nerve supply.

In the preceding theoretical account I have endeavoured to state as briefly as possible the issues which seem to me to be involved. In view of the numerous points which require experimental investigation, a full discussion would clearly be premature.

General results and conclusions.

Nicotine causes in certain muscles of the fowl prolonged contraction. The muscular contraction is also obtained after section of the nerves to the muscle and after paralysis of the nerves by nicotine or by curari.

The nicotine contraction is diminished by injection of a sufficient dose of curari. The two poisons are mutually antagonistic as regards stimulating effect on the muscles; but the action of nicotine is more powerful than that of curari.

At the height of the nicotine contraction a galvanic current causes partial inhibition.

Degeneration of the nerves supplying the muscles leaves essentially unaltered the effects described above; but there is evidence of an

[1] I consider that there are intrinsic differences in both, which are independent of one another.

increased responsiveness to nicotine. The action of curari is less marked, but that may be due to an increased sensitiveness to nicotine.

Since there is evidence that the axon-endings in skeletal muscle degenerate after section of the nerves supplying the muscle, I conclude that nicotine and curari do not act on the axon-endings but on the muscle itself. Further, since both nicotine and curari prevent nervous impulses from affecting the contractile substance, but do not prevent the muscle from contracting on direct stimulation, I conclude that the poisons do not act directly on the contractile substance, but on other substances in the muscle which may be called receptive substances.

The evidence with regard to striated muscle seems to me to be on a sufficiently firm basis to allow the deductions drawn from it to be applied to other cells, with regard to which there is more or less evidence of a similar kind.

Thus there is evidence that the majority of substances which are ordinarily supposed to act upon nerve-endings (as nicotine, curari, atropine, pilocarpine, strychnine) act upon the receptive substances of the cells.

And as adrenalin, an internal secretion, acts upon receptive substance, it is probable that secretin, thyroidin, and the internal secretion formed by the generative organs, also act on receptive substances, although in these cases the cells may be unconnected with nerve fibres.

So we may suppose that in all cells two constituents at least are to be distinguished, a chief substance, which is concerned with the chief function of the cell as contraction and secretion, and receptive substances which are acted upon by chemical bodies and in certain cases by nervous stimuli. The receptive substance affects or is capable of affecting the metabolism of the chief substance.

A study of the action of different poisons shows—on the theory just given—that the receptive substance of cells, even of the same class, varies considerably. This I consider is mainly due to an inherent tendency to variation in the chemical nature of the cells, so that even in the same class of cell the receptive substances formed are commonly not identical.

In unstriated muscle and glands the innervation varies widely in degree, and in some cases no nervous action can be shown; this difference may, I think, reasonably be attributed primarily to a different responsiveness to nervous stimuli of the receptive substances, and it seems to me possible that in some cases nerve-endings are present which are unable to influence the cell. No doubt such ineffective

nerves would tend to disappear by natural selection. No doubt also, when a nerve is effective, the frequency with which it is put in action would tend to increase the receptive substance by use (just as the cell as a whole is increased by use) and so to check the tendency in the cell to further chemical change.

The different degree of tone of the tissues is probably also in part due to the responsiveness of the receptive substance.

Many chemical bodies show a more or less marked preference for the receptive substance connected with certain classes of nerves. And this is the case also, when a tissue (unstriated muscle and gland cells) is innervated from two different systems of nerves. This preference I connect with a similarity in the receptive substance due to each system of nerves becoming functionally connected with cells at approximately the same time in phylogenetic development. The conditions leading to the formation of receptive substance would be in general similar, and the receptive substance of many of the cells would have common characters. These tend to become fixed by use.

The fundamental point of the views here put forward, viz. that the poisons act on some constituent of the cells and not on the nerve-endings, is the same as that put forward earlier in relation to the action of nicotine on nerve cells and of adrenalin on unstriated muscle and glands. But at that time I did not see my way to decide what constituent of the cell was acted on. The subsequent work mentioned in the Introduction, and especially that of Elliott on the action of adrenalin, made the issues clearer. Elliott does not agree with my conclusion that adrenalin acts on unstriated muscle, but so far as the state of things in the adult is concerned, the difference is verbal, since he regards the substance acted on as being in trophic dependence on the muscle. This substance he places, as did Brodie and Dixon, at the junction of the nerve with the muscle proper. With this conclusion I agree up to a certain point. On my view, the myo-neural junction is a part of the receptive substance localized in the neighbourhood of the axon-ending, and I think it unlikely that in all cases of axon-endings the receptive substance occurs only as a connecting link. Elliott's suggestion that the motor or inhibitory effect upon a cell depends upon the nature of the myo-neural junction is, I think, sound. And, to put the matter in more general terms, I consider that a cell may make motor or inhibitory receptive substances or both, and that the effect of a nervous impulse depends upon the proportion of the two kinds of receptive substance which is affected by the impulse.

With Elliott's view that the myo-neural junction is developed solely in consequence of nerve union I do not agree, chiefly because the myo-neural junction does not degenerate on degeneration of its nerve. And the early action of certain poisons on the embryo seems to me against this view. Further, the action of poisons in the adult shows considerable differences on the receptive substance connected with the same system of nerves, and some resemblances in the receptive substance connected with certain nerves belonging to different systems. It is clear then that the nerve fibres of a given system on union with cells do not give rise to the same synaptic substance. Hence the dissimilarity of the synaptic substance must be due to intrinsic differences either in the nerve fibres belonging to any one system, or in the cells in which they end. On the whole the latter alternative seems to me more probable.